# Latent TB: Challenges for diagnosis and treatment

**Edward N. Robinson, Jr. MD MPH**
**Medical Director, Guilford County Department of Public Health**

## Roadmap

- **Pathogenesis of TB**
- Historical Perspective
- Epidemiology and Trends
- Tests for Latent TB
- Treatment for Latent TB
- What makes a successful program for LTBI-Tx

Arches National Park, Utah
March 2011

## Tuberculosis Transmission

- Caused by: *Mycobacterium tuberculosis*
- Spread by: Airborne route
  Droplet nuclei
- Affected by: Infectiousness of patient
  Environmental conditions
  Duration of exposure
- Most persons exposed do not become infected

CDC

## "It" Happens in 2 Ways

- Disjoint Probabilities
- Conjoint Probabilities

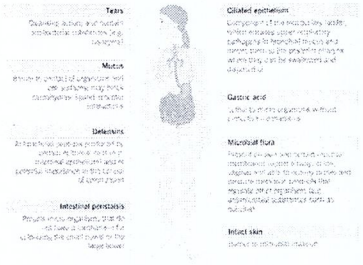
## Disjoint Probabilities

- Finite probability over incremental periods of time
- Individual period....probability is low
- BUT, given enough increments, probability approaches certainty
- People underestimate disjoint probabilities

## Disjoint Probabilities 1906 San Francisco

http://www.sfmuseum.org/

## Barrier Defenses




Armstrong and Cohen 1999

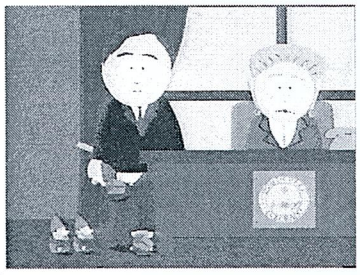
Department of Public Health

## Conjoint Probabilities

- Outcome dependent upon a series of linked events
- Each event has individual probability of happening
- If one link does not occur, then outcome does not occur
- People overestimate conjoint probabilities

Department of Public Health

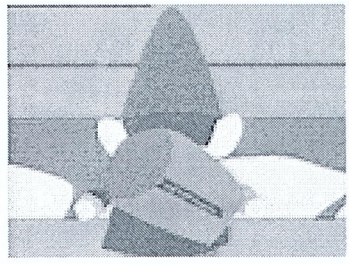
## Underpants Gnomes



Department of Public Health

http://www.comedycentral.com

## Underpants Gnomes



Department of Public Health

http://www.comedycentral.com

## Underpants Gnomes

- Step One. Steal Underpants
- Step Two……
- Step Three. Profits!!!

Department of Public Health

http://www.comedycentral.com

## The College Student


Department of Public Health

## Tuberculosis Transmission

- Caused by: *Mycobacterium tuberculosis*
- Spread by: Airborne route
  Droplet nuclei

- Affected by: Infectiousness of patient
  Environmental conditions
  Duration of exposure
- Most persons exposed do not become infected

CDC

Department of Public Health

## Pathogenesis
## Latent *M. tuberculosis* Infection

- Inhaled droplet nuclei with *M. tuberculosis*
  - Reach alveoli
  - Are taken up by alveolar macrophages
  - Reach regional lymph nodes
  - Enter bloodstream and disseminate
- Chest radiograph may have transient abnormalities
- Specific cell-mediated immune response controls further spread

CDC

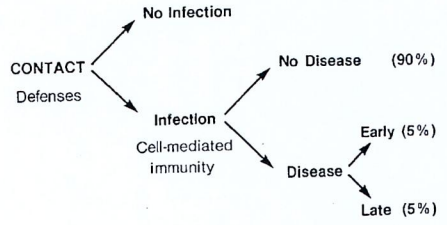
Department of Public Health

## Pathogenesis – As a general rule

- Infection is dependent upon exogenous factors.
  - Cavitary smear positive source
  - Indoor, confined environment
  - Prolonged exposure
- Disease is dependent upon endogenous factors.
  - Immunity

Department of Public Health

## Outcome of TB exposure




Department of Public Health

Murray: Am Rev Respir Dis 1989;140:1788-1795

## Pathogenesis
## Active TB Disease

- Latent *M. tuberculosis* infection progresses to active TB in
  - A very small number of persons soon after infection (primary progression)
  - About 5% of infected persons within first 2 years after infection
  - About 5% of infected persons at some time later in life
- Risk of progression greatest in first 2 years after infection
- Risk greater if cell-mediated immunity impaired

CDC

Department of Public Health

## Major Questions – 10% of infection progresses to disease

- ...but is this an historic or current figure?
  - Citation in 1970s textbook
- ...have times changed?
  - If disease is reflective of underlying immunity, is the underlying resistance to TB greater now?
    - Longer lived.
    - Better nutrition.

Department of Public Health

## Major Questions – 10% of infection progresses to disease

- We know that active TB is most common in the first years of entry into the country.
- What happens after these few years?
  - Nutrition changes
  - Environmental changes

Department of Public Health

## Obesity is associated with a lower risk of active pulmonary TB in older population (Hong Kong).

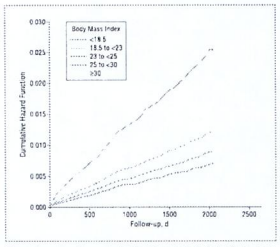



Figure. Hazard function curves of active tuberculosis for different body mass index categories in the overall sex model.

Department of Public Health

Leung et al. Arch Intern Med. 2007;167:1297-1304

## TB Then
## Hester Street ("Pig-Market") 1890

Three Centuries of Infectious Disease

Department of Public Health

## TB Then

An illustration from the mid-1800s depicts squalid tenement conditions targeted by New York reformers in an anti-TB crusade.

Department of Public Health

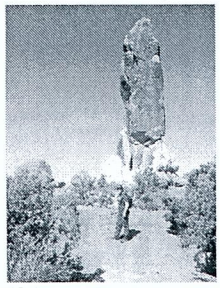
Chowder: Smithsonian Magazine

## Nepalese Refugee Camp

Department of Public Health

## Roadmap

- Pathogenesis of TB
- **Historical Perspective**
- Epidemiology and Trends
- Tests for Latent TB
- Treatment for Latent TB
- What makes a successful program for LTBI-Tx



Department of Public Health

Dark Angel, Arches National Park, Utah March 2011

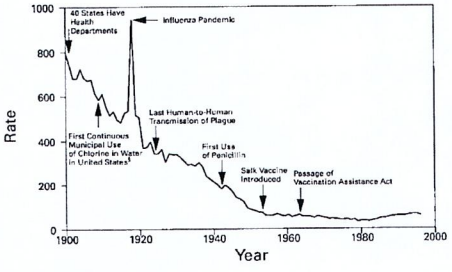
## So...


## TB Then

- 1945
  - 63,000 deaths due to tuberculosis
  - 115,000 new cases (87/100,000 persons)
  - Tuberculin surveys
    - 50% population infected
  - 450 hospitals/79,000 beds
  - Case fatality rate for cavitary tuberculosis 50% at 5 years

Snider: Annals Intern Med 1997:126:237

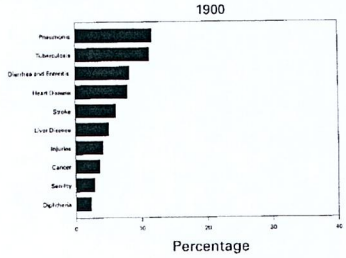
## Historical Death Rate




MMWR 1999:48:621

## TB Then

FIGURE 2. The 10 leading causes of death as a percentage of all deaths — United States, 1900 and 1997



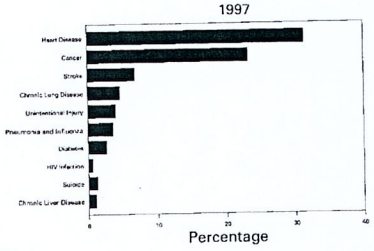

MMWR 1999:48:623

## The Tools of Public Health

- Quarantine/Isolation
- Vaccination
- Sanitation
- Antibiotics
- Education

Glass R et al. N Engl J Med 2009;361:1776-1785

## TB Now




MMWR 1999:48:623

## The Tools of Public Health

- Quarantine/Isolation
- Vaccination
- Sanitation
- Antibiotics
- **Education**

Department of Public Health

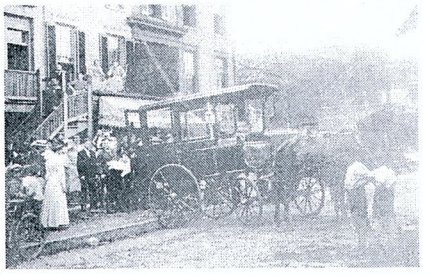
Glass R et al. N Engl J Med 2009;361:1776-1785

## TB Then
## John Keats, Death Bed Portrait by Joseph Severn

Department of Public Health

Plague, Pox & Pestilence

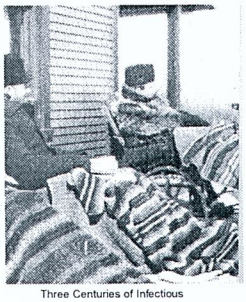
## TB Then
## 1908 St. Paul, Minnesota



Department of Public Health

Three Centuries of Infectious Disease 1998

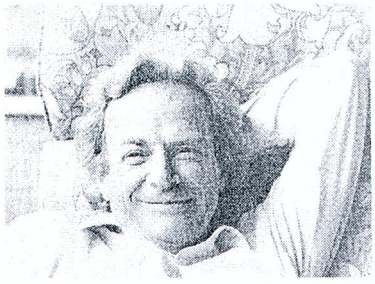
## TB Then
## Saranac Lake 1894



Department of Public Health

Three Centuries of Infectious Disease

## TB Then and Now



Department of Public Health

Sykes: 1994

## TB Then and Now

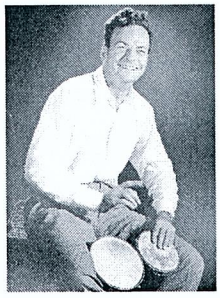
Department of Public Health

Sykes: 1994

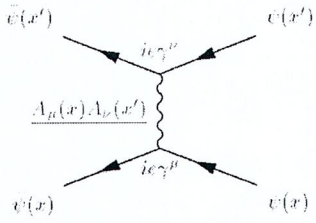
## Challenger Disaster

http://deceng.files.wordpress.com/2007/11/feynman-challenger.jpg

## Renaissance Man



## Feynman Diagrams



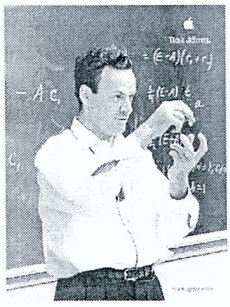

## Feynman Diagrams

## Richard Feynman Quote

- Physics is like sex;
- It may give some practical results, but that's not why we do it.

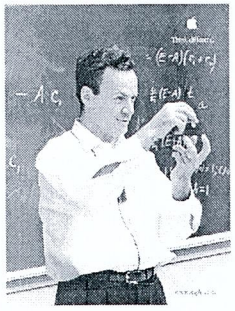
## Richard Feynman

- Some years ago I had a conversation with a layman about flying saucers — because I am scientific I know all about flying saucers!
- I said "I don't think there are flying saucers'.



## Richard Feynman

- So my antagonist said, "Is it impossible that there are flying saucers? Can you prove that it's impossible?"



Department of Public Health

## Richard Feynman

- "No", I said, "I can't prove it's impossible. It's just very unlikely".
- At that he said, "You are very unscientific. If you can't prove it impossible then how can you say that it's unlikely?"

Department of Public Health

## Richard Feynman

- But that is the way that is scientific.
- It is scientific only to say what is more likely and what less likely, and not to be proving all the time the possible and impossible.

Department of Public Health

## Richard Feynman

- To define what I mean, I said to him:

"Listen, I mean that from my knowledge of the world that I see around me, I think that it is much more likely that the reports of flying saucers are the results of the known irrational characteristics of terrestrial intelligence than of the unknown rational efforts of extra-terrestrial intelligence."

Department of Public Health

## TB Then and Now

Sykes: 1994

Department of Public Health

## TB Then and Now

Sykes: 1994

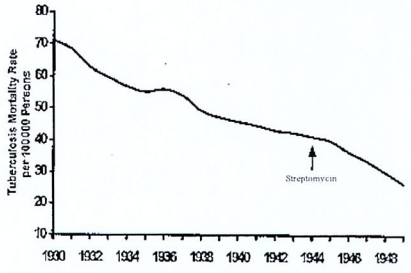
Department of Public Health

## TB Then
## Selman Waksman 1944

Department of Public Health

Three Centuries of Infectious Disease 1998

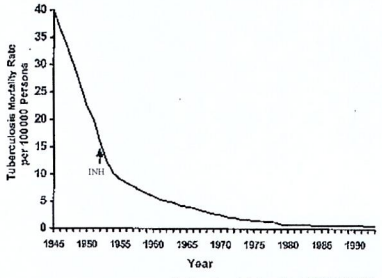
## TB Then




Department of Public Health

Snider: Annals Intern Med 1997:126:237

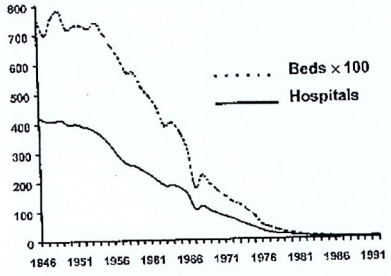
## TB Then




Department of Public Health

Snider: Annals Intern Med 1997:126:237

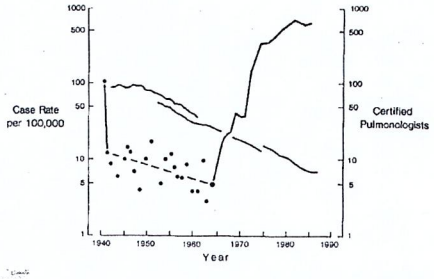
## TB Then




Department of Public Health

Snider: Annals Intern Med 1997:126:237

## TB Then

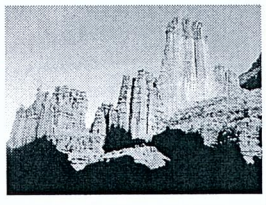



Department of Public Health

Murray Am Rev Respir Dis 1989;140:1788-95

## Roadmap

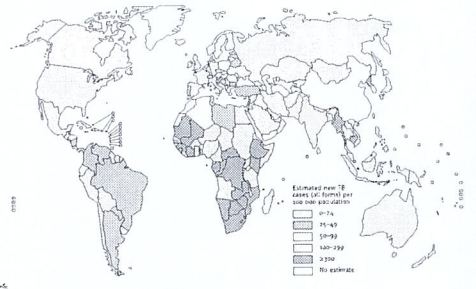
- Pathogenesis of TB
- Historical Perspective
- **Epidemiology and Trends**
- Tests for Latent TB
- Treatment for Latent TB
- What makes a successful program for LTBI-Tx



Department of Public Health

Fisher Towers State Park, Utah, March 2011

## Estimated TB Incidence Rates. 2009



WHO 2010

## Estimates of TB Cases – 2008

- Incidence 9.4 million cases
  - 55% Asia
    - China
    - India
    - Indonesia
  - 30% Africa
    - South Africa
    - Nigeria

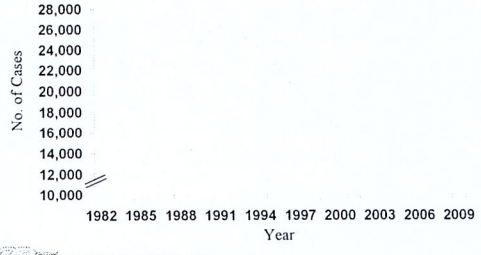
www.who.int

## Estimates of TB Cases – 2008

- Mortality
  - 1.3 million deaths
- MDR-TB
  - 0.5 million cases
    - Europe accounts for 85%
- XDR-TB scattered

www.who.int

## Reported TB Cases* United States, 1982–2009



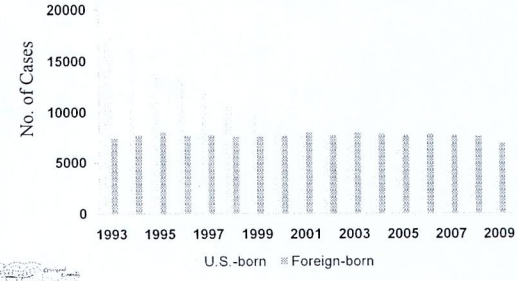

*Updated as of July 1, 2010.

## TB Morbidity United States, 2003–2009

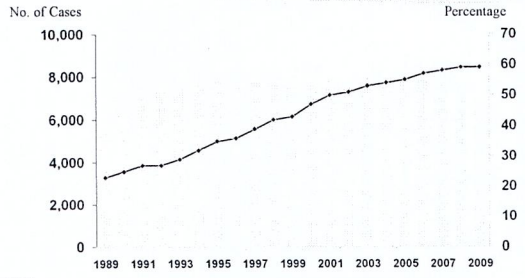
| Year | No. | Rate* |
|---|---|---|
| 2003 | 14,836 | 5.1 |
| 2004 | 14,499 | 4.9 |
| 2005 | 14,064 | 4.8 |
| 2006 | 13,734 | 4.6 |
| 2007 | 13,280 | 4.4 |
| 2008 | 12,906 | 4.2 |
| 2009 | 11,545 | 3.8 |

*Cases per 100,000, updated as of July 1, 2010.

## Number of TB Cases in U.S.-born vs. Foreign-born United States, 1993–2009

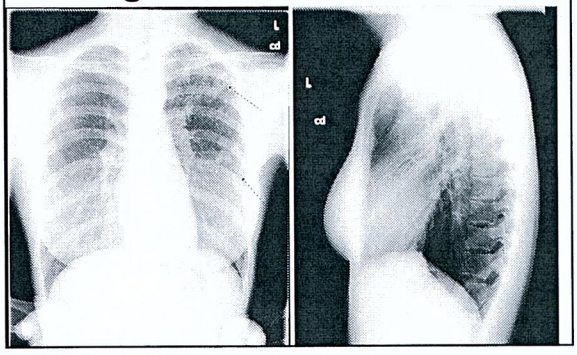


## Trends in TB Cases in Foreign-born Persons, United States, 1989–2009

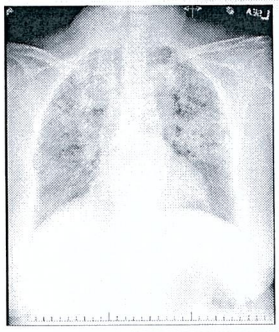



Department of Public Health

## College Student

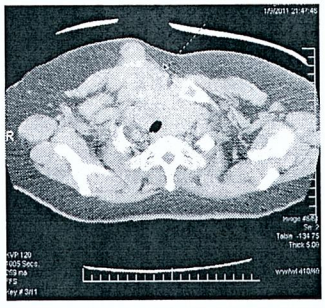


## WOMAN FROM SUDAN



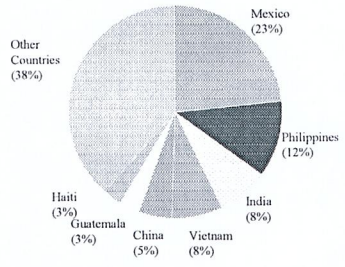
Department of Public Health

## WOMAN FROM SUDAN



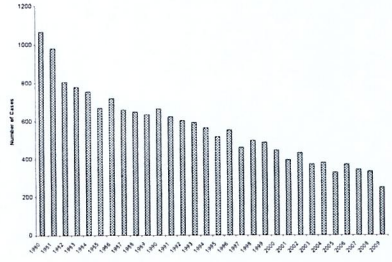
Department of Public Health

## Countries of Birth of Foreign-born Persons Reported with TB United States, 2009




Department of Public Health

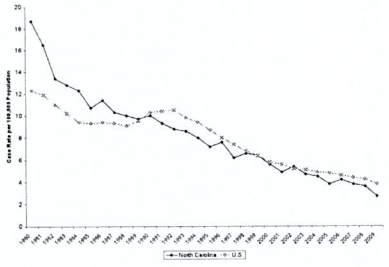
## Reported TB Cases in NC: 1980-2009



Department of Public Health

www.epi.state.nc.us/epi/tb/

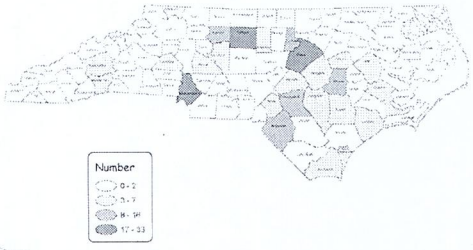
## TB Case Rates for N.C. and the US: 1980-2009




Department of Public Health

www.epi.state.nc.us/epi/tb/

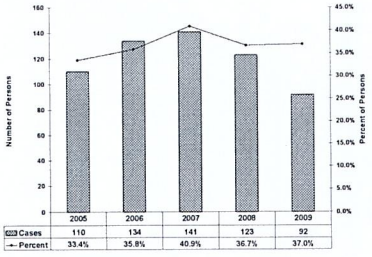
## North Carolina 2009 Tuberculosis Cases




Department of Public Health

www.epi.state.nc.us/epi/tb/

## NC Foreign-Born TB Cases: 2005-2009

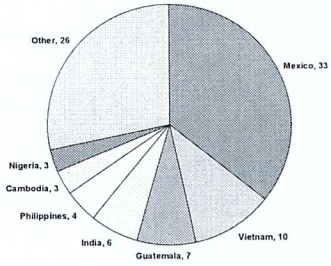



| | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|
| Cases | 110 | 134 | 141 | 123 | 92 |
| Percent | 33.4% | 35.8% | 40.9% | 36.7% | 37.0% |

Department of Public Health

www.epi.state.nc.us/epi/tb/

## Countries of Origin for 2009 Foreign-born TB cases in NC




Department of Public Health

www.epi.state.nc.us/epi/tb/

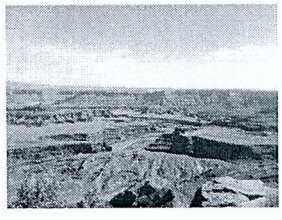
## Elimination of TB

- Conjunctive Probability
  - Intervene at <u>one</u> point
- Before the development of Active Disease
  - Detection of latent disease

Department of Public Health

## Roadmap

- Pathogenesis of TB
- Historical Perspective
- Epidemiology and Trends
- **Tests for Latent TB**
- Treatment for Latent TB
- What makes a successful program for LTBI-Tx



Department of Public Health

Dead Horse State Park, Utah, March 2011

## Robert Koch's BIG MISTAKE

German researcher Robert Koch found microorganism that causes TB in 1882

Department of Public Health

Chowder: Smithsonian Magazine

## The Mistake

- 1890 - Robert Koch announced a "cure" for tuberculosis

  A brownish transparent filtrate of *Mycobacterium tuberculosis* injected subcutaneously daily.

Department of Public Health

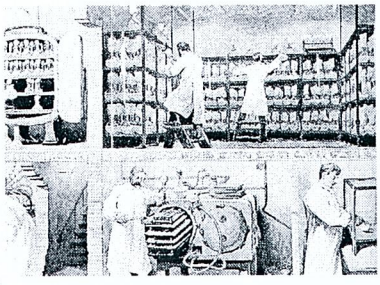
Clin Infect Diseases 1993:17:968-75

## TB Skin Test Koch's Tuberculin


Department of Public Health

Three Centuries of Infectious Disease

## TB Skin Test Koch's Tuberculin



Department of Public Health

Kiple Plague, Pox & Pestilence 1997

## TB Skin Test Koch's Tuberculin


Department of Public Health

Three Centuries of Infectious Disease

## Koch's Tuberculin Institute for Infectious Diseases Berlin 1891

Department of Public Health

Three Centuries of Infectious Disease

## Introduction

- 1890 - Robert Koch announced a "cure" for tuberculosis
- 1891 - "Cure" disproved...but the tuberculin skin test was born

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Not the only time Koch was "wrong"

- In 1901, he stated that "the human subject is immune against infection by bovine bacilli...that I do not consider it necessary to take any measures to conteract the risk of infection"

Department of Public Health

Grange and Zumla, Tuberculosis 2009

## Not the only time Koch was "wrong"

- Fortunately...he was speaking to Brits.

Department of Public Health

Grange and Zumla, Tuberculosis 2009

## Methods of administration

- Pirquet cutaneous test
- Moro percutaneous patch test
- Calmette conjunctival test
- Mantoux intracutaneous test

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Tuberculins Old Tuberculin Recipe

- Grow M. tb in glycerinated meat broth (or Sauton's media)
- Kill the organisms by heating in 100oC steam cabinet
- Concentrate with evaporation to 1/10 original
- Inject into any passing human

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Tuberculins Old Tuberculin

It would surely simplify life for manufacturers if OT were plainly described as any witches' brew derived by evaporation of any unspecified fluid medium in which any unspecified strain of mammalian M. tb had been grown, provided its potency matched that of another witches' brew kept in Copenhagen....

Green 1951

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Methods of Skin Testing
## Multiple-puncture tests (MPTs)

School nurse administers TB tests to wary Ohio kindergartners in 1966.

Chowder. Smithsonian Magazine

## Methods of Skin Testing
## Multiple-puncture tests (MPTs)

- Advantage to speed and ease of adminstration
- Screen large populations of low tuberculin reactivity
- Limited by variability of tuberculin delivery
- Confirmation with Mantoux necessary

Clin Infect Diseases 1993:17:968-75

## Tuberculins
## PPD Recipe

- Precipitate culture filtrates of tb with ammonium sulfate or with trichloracetic acid
- Standardize against Tuberculin PPD lot number 49608 (PPD-S) prepared in 1941:
  - 1 TU = 0.00002 mg of PPD-S
- Add Tween 80

Clin Infect Diseases 1993:17:968-75

## Tuberculin Skin Test

- 1976 – FDA appointed a Panel on Skin Test Antigens
- Only two passed
  - Tubersol (Connaught)
  - Aplisol (Parke Davis)

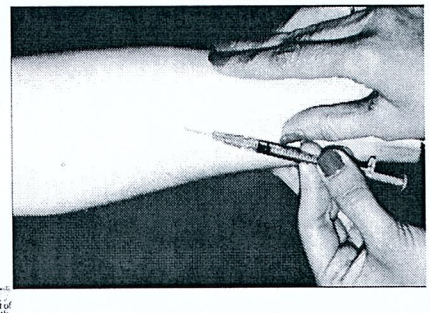
Daley, Denver TB Course, 2010

## Methods of Skin Testing
## Mantoux

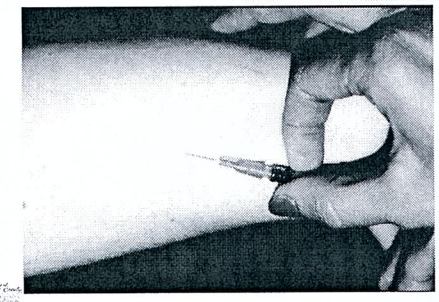
- Intracutaneous injection of 5 TU into the volar surface of the forearm

Clin Infect Diseases 1993:17:968-75

## Methods of Skin Testing
## Mantoux



## Methods of Skin Testing
## Mantoux



Department of Public Health

## Methods of Skin Testing
## Mantoux

Department of Public Health

## Methods of Skin Testing
## Mantoux

- read at 48-72 hours
  - "standard" palpation
  - alternative pen method

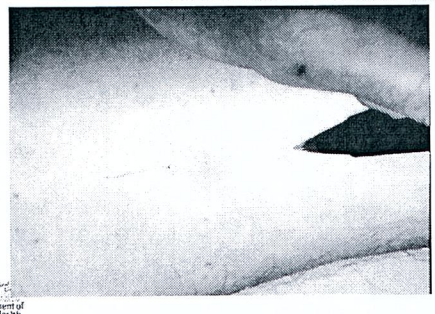
Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Methods of Skin Testing
## Mantoux

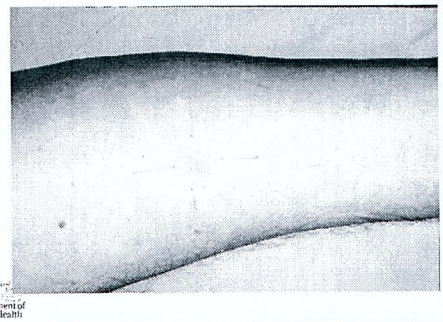
Department of Public Health

## Methods of Skin Testing
## Mantoux



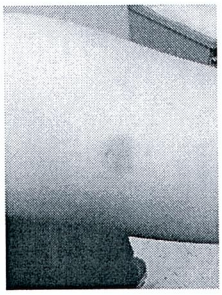
Department of Public Health

## Methods of Skin Testing
## Mantoux



Department of Public Health

## Skin Testing Mantoux - Negative



Department of Public Health

## Distribution of Skin Test Reaction

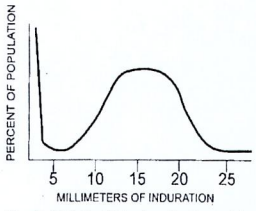



Figure 1. Distribution of tuberculin reactions in a population with few cross-reactions. Reprinted from [18] by courtesy of Marcel Dekker, Inc.

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Distribution of Skin Test Reaction

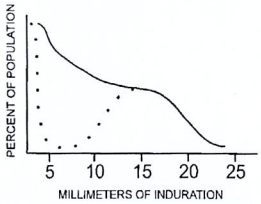


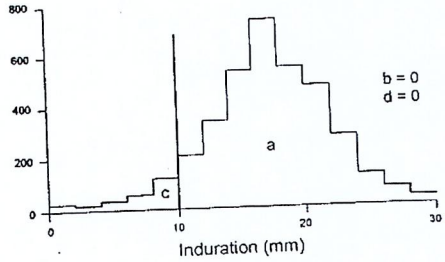

Figure 2. Distribution of tuberculin reactions in a population with relatively frequent cross-reactions. A hypothetical subpopulation of true tuberculin reactors, with a distribution similar to that shown in figure 1, is indicated by the dotted line. Reprinted from [18] by courtesy of Marcel Dekker, Inc.

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Frequency of tuberculin reactors - 3,826 TB patients

**1950s**

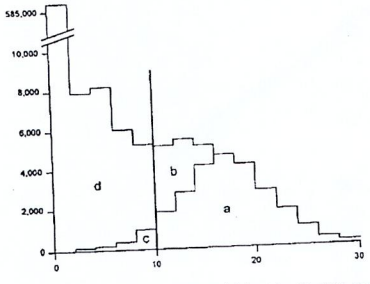



Department of Public Health

Rose et al. J Gen Intern Med 1995;10:635-42.

## Frequency of tuberculin reactors - 643,694 US Navy recruits

**1958-1964**




Department of Public Health

Rose et al. J Gen Intern Med 1995;10:635-42.

## Accuracy of Skin Tests False Positive

- Nontuberculous mycobacterium
- bacille Calmette-Guérin (BCG)
- Invalid Interpretation

Department of Public Health

Clin Infect Diseases 1993:17:968-75

## Ward's Version of Bayes Theorem

- p(D|T) ≅ p(D)x p(T|D)/p(T)

Department of Public Health

## Ward's Version of Bayes Theorem

- p(D|T) ≅ p(D)x p(T|D)/p(T)
- P(D) is the pretest probability of infection (the prevalence of the disease)
- P(T|D) is the sensitivity of the test
- P(T) is the specificity of the test

Department of Public Health

## Accuracy of Skin Tests Bayes Theorem

**Table 1.** Impact of the prevalence of infection with *M. tuberculosis* on the predictive value of a positive tuberculin test.

| | Predictive value at indicated specificity* | |
|---|---|---|
| Prevalence (%) | 0.95 | 0.99 |
| 90 | 0.99 | 0.999 |
| 50 | 0.95 | 0.99 |
| 25 | 0.86 | 0.97 |
| 10 | 0.67 | 0.91 |
| 5 | 0.50 | 0.83 |
| 1 | 0.16 | 0.49 |
| 0.1 | 0.03 | 0.10 |
| 0.01 | 0.002 | 0.09 |

* For these calculations the sensitivity of the tuberculin test is assumed to be 100%.

Clin Infect Diseases 1993:17:968-75

Department of Public Health

## Remember Koch's Second Mistake?

- Bovine TB elimination

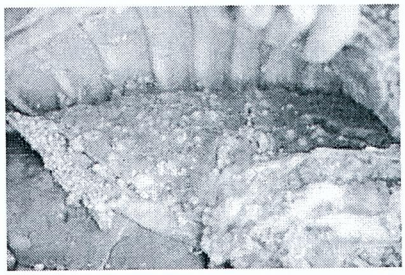
Department of Public Health

## Bovine TB elimination

- Tuberculin testing of cattle for bovine TB
- Kill those cows positive
- Examine the remains

Department of Public Health

## Pearl Disease



Department of Public Health

## Prevalence of bovine TB fell

- At the end of WWII, estimates were that 30-35% of dairy cows in UK were reactive.
- Compulsory test-and-slaughter began in 1951.
- By 1979, only 0.18% of herds contained infected animals (a problem of badgers).

Grange and Zumla, Tuberculosis, 2009

## Prevalence of bovine TB fell

- Problem is that as prevalence falls, tuberculin tests began detecting cows with no clinical disease.
- What you get is Angry farmers.

## humans...we get the same problem.

- We can't do "that" to humans.
- Their family members would get angry too.

## Problem of BCG

- CDC asks us to ignore this part

## Booster Phenomenon

- Two skin tests applied 1-3 weeks apart
  - First is negative
  - Second is positive
- The "boosting" of a previous exposure
- A Reactor...not a converter

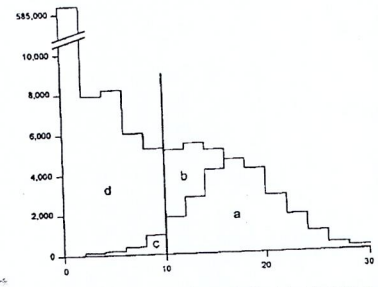
Clin Infect Diseases 1993:17:968-75

## Criteria for tuberculin positivity, by risk group

| Reaction ≥5 mm of induration | Reaction ≥10 mm of induration | Reaction ≥15 mm of induration |
|---|---|---|
| Human immunodeficiency virus (HIV)-positive persons | Recent immigrants (i.e., within the last 5 yrs) from high-prevalence countries | Persons with no risk factors for TB |
| Recent contacts of tuberculosis (TB) case patients | Injection drug users | |
| Fibrotic changes on chest radiograph consistent with prior TB | Residents and employees* of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters | |
| Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)* | Mycobacteriology laboratory personnel | |
| | Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass | |
| | Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high risk | |

MMWR June 9,2000

## Frequency of tuberculin reactors - 643,694 US Navy recruits
1958-1964




Rose et al. J Gen Intern Med 1995;10:635-42.

## Ward's Version of Bayes Theorem

- $p(D|T) \cong p(D) \times p(T|D)/p(T)$

## Is there an alternative to TB Skin Tests?

Comparison of a Whole-Blood Interferon γ Assay With Tuberculin Skin Testing for Detecting Latent *Mycobacterium tuberculosis* Infection


Gerald H. Mazurek, MD
Philip A. LoBue, MD
Charles L. Daley, MD
John Bernardo, MD
Alfred A. Lardizabal, MD
William R. Bishai, MD, PhD
Michael F. Iademarco, MD, MPH
James S. Bothel, PhD



**Context** Identifying persons with latent tuberculosis infection (LTBI) is crucial to the goal of TB elimination. A whole-blood interferon γ (IFN-γ) assay, the QuantiFERON-TB test, is a promising in vitro diagnostic test for LTBI that has potential advantages over the tuberculin skin test (TST).

**Objectives** To compare the IFN-γ assay with the TST and to identify factors associated with discordance between the tests.

**Design and Setting** Prospective comparison study conducted at 5 university-affiliated sites in the United States between March 1, 1998 and June 30, 1999.

**Participants** A total of 1226 adults (mean age, 39 years) with varying risks of *Mycobacterium tuberculosis* infection or documented or suspected active TB, all of whom


JAMA 2001;286:1740-7

## Possible Consequences of Switching from Old to New Reference Tests

| New Reference Test | Old Reference Test: Positive | Old Reference Test: Negative |
|---|---|---|
| Positive | A. Agreement; no change in management | B. Apparent cases detected only by the new test |
| Negative | C. Apparent cases detected only by the old test | D. Agreement; no change in management |

Glasziou et al. Ann Intern Med. 2008;149:816-821.

## Performance of New Test if (I) More Sensitive or (II) More Specific

| New Reference Test | Old Reference Test: Positive | Old Reference Test: Negative |
|---|---|---|
| I. New test possibly more sensitive | | |
| Positive | A. Agreement | B. Apparent new cases |
| Negative | C. Nil | D. Agreement |
| II. New test possibly more specific | | |
| Positive | A. Agreement | B. Nil |
| Negative | C. Apparent non-cases | D. Agreement |

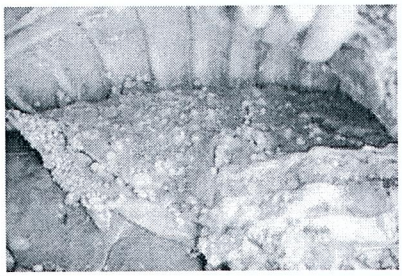
Glasziou et al. Ann Intern Med. 2008;149:816-821.

## Disagreements Between Old and New Tests

- Principle 1: The consequences of the new reference test can be understood through the disagreements between the old and new reference tests.
- Principle 2: Resolving the disagreements between old and new tests requires a fair, but not necessarily perfect, umpire test.

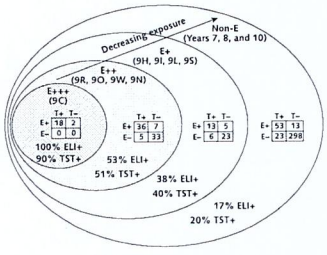
Glasziou et al. Ann Intern Med. 2008;149:816-821.

## Pearl Disease



Department of Public Health

## Results of 2 tests for tuberculosis, stratified by exposure to the index case.

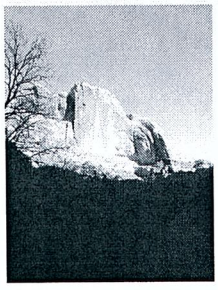



Department of Public Health

Glasziou et al. Ann Intern Med. 2008;149:816-821.

## Roadmap

- Pathogenesis of TB
- Historical Perspective
- Epidemiology and Trends
- Tests for Latent TB
- **Treatment for Latent TB**
- What makes a successful program for LTBI-Tx



Department of Public Health

Moab, Utah, March 2011

## What to do with a positive?

- Persons at greatest risk for progression to active tuberculosis disease included
  - those with HIV infection (the greatest single risk factor for progression)
  - recent tuberculosis infection
  - immigrants with LTBI from high endemic areas (especially within their first year in the United States)...

Department of Public Health

Blumberg, Ann Int Med 2008;149:761

## What to do with a positive?

- ...and those with LTBI and selected underlying illnesses (for example, silicosis, diabetes mellitus, chronic renal failure, some malignant conditions, and immunosuppressive medications)

Department of Public Health

Blumberg, Ann Int Med 2008;149:761


## What to do with a positive?

- ...and those with LTBI and selected underlying illnesses (for example, silicosis, diabetes mellitus, chronic renal failure, some malignant conditions, and immunosuppressive medications)

Department of Public Health

Blumberg, Ann Int Med 2008;149:761

## Acceptable Regimens for Treatment of LTI

| Drugs | Duration (mo) | Interval | Rating* (Evidence)† HIV- | HIV+ |
|---|---|---|---|---|
| Isoniazid | 9 | Daily | A (II) | A (II) |
| | | Twice weekly | B (II) | B (II) |
| Isoniazid | 6 | Daily | B (I) | C (I) |
| | | Twice weekly | B (II) | C (I) |
| Rifampin–pyrazinamide | 2 | Daily | B (II) | A (I) |
| | 2–3 | Twice weekly | C (II) | C (I) |
| Rifampin | 4 | Daily | B (II) | B (III) |

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.
† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

Department of Public Health

MMWR June 9,2000

## What to do with a positive?

- The current recommendations for treatment of LTBI often seem more faith-based than evidence-based.

Department of Public Health

Blumberg, Ann Int Med 2008;149:761

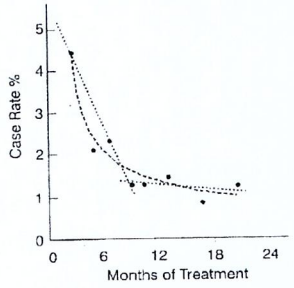
## What to do with a positive?

- Despite substantial data on the use and efficacy of isoniazid for treating LTBI (>20 randomized, controlled trials involving >100 000 persons), the recommendation for 9 months of isoniazid does not come directly from any randomized trials (for example, comparing 9 months with 6 or 12 months of therapy), but from reanalysis of data collected 50 years ago.

Department of Public Health

Blumberg, Ann Int Med 2008;149:761

## Duration of INH therapy




Department of Public Health

MMWR June 9,2000

## What about INH Hepatotoxicity?

- Data is twenty years old
  - 5-20 cases/1000
    - 1-10% case fatality
- Diagnosis usually based on mild increase enzymes
  - 10-20% initiates

Department of Public Health

JAMA 1999;281:1014-8

**INH Hepatotoxicity**
**Nolan, Goldberg, Buskin at Seattle-King County Public Health Department**

- Monthly visits for medication refills and evaluations
- Diagnosis of hepatotoxicity
  - Symptoms
    - anorexia, nausea, vomiting, jaundice
  - AST 5X normal
  - Resolution with cessation of therapy

Department of Public Health

JAMA 1999;281:1014-8

**INH Hepatotoxicity**
**Nolan, Goldberg, Buskin at Seattle-King County Public Health Department**

- 11,141 Patients started INH therapy for latent infection
  - 11 developed hepatotoxicity
    - median age 34 (27-67)
    - 73% female
    - median interval from start to diagnosis 9 weeks
      - range 19 days to 5 months
      - 91% within 3 months

Department of Public Health

JAMA 1999;281:1014-8

**INH Hepatotoxicity**
**Nolan, Goldberg, Buskin at Seattle-King County Public Health Department**

- 11,141 Patients started INH therapy for latent infection
  - 1 patient hospitalized with hepatotoxicity
  - No deaths
  - All recovered without sequelae

Department of Public Health

JAMA 1999;281:1014-8

**INH Hepatotoxicity**
**Nolan, Goldberg, Buskin at Seattle-King County Public Health Department**

- 1,427 Patients started INH in multidrug regimen
  - 15 developed hepatitis
    - median age 41 (15-78)
    - 60% female
  - 7 had cofactors (Tylenol, viral hepatitis)
  - One death of fulminate hepatitis B

Department of Public Health

JAMA 1999;281:1014-8

## INH Hepatotoxicity - Conclusions

- By following CDC Guidelines, age of INH recipients reduced compared with 20 years ago.
- No routine testing of enzymes needed
- INH is a safe drug

Department of Public Health

JAMA 1999;281:1014-8

**INH Hepatotoxicity -Versi on 2**
**THE HEALTH CARE WORKER**

- Stuart, Wilson, Grayson at Monash Medical Centre, Prahran, Australia
- HCW with a positive PPD
  - ≥ 15 mm with history of BCG
  - ≥ 10 mm without BCG
- Baseline and monthly serum enzymes

Department of Public Health

Clinical Infectious Diseases 1999;28:895-7

**INH Hepatotoxicity -Versi on 2**
**THE HEALTH CARE WORKER**

- 878 HCW (89% history of BCG)
  - 299 were PPD reactive
  - 83 (28%) elected INH
    - median age 39 (25-56)
    - 73 female
  - 30 (35%) stopped drug
    - 26 (87%) because of toxicity

Department of Public Health

Clinical Infectious Diseases 1999;28:895-7

## INH Hepatotoxicity -Versi on 2
## THE HEALTH CARE WORKER

- Conclusion: INH is a toxic drug.
- "Preventive therapy with isoniazid has an important role, and guidelines for such therapy have been defined. Nevertheless, the relatively high rate of symptomatic and asymptomatic toxicity noted in this study is worth considering when prescribing INH prophylaxis...we advocate the use of monthly liver function testing....

Department of Public Health

Clinical Infectious Diseases 1999;28:895-7

**Severe Isoniazid- Associated Liver Injuries Among Persons Being Treated for Latent Tuberculosis Infection— United States, 2004-2008**

- During 2004-2008, a total of 17 serious liver injuries were reported in patients receiving INH therapy
- Five patients underwent liver transplantation
- Five died, including one liver transplant recipient.

Department of Public Health

MMWR. 2010;59:224-229

**Severe Isoniazid- Associated Liver Injuries Among Persons Being Treated for Latent Tuberculosis Infection— United States, 2004-2008**

- Calculation of INH-associated SAE rates is made difficult by the absence of reliable denominators for the number of persons initiating INH treatment, which has been estimated at 291,000 to 433,000 per year.

Department of Public Health

MMWR. 2010;59:224-229

## What about alternatives to INH?

- Very limited data are available on the efficacy of rifampin for treating LTBI, with most reports being small case series or programmatic evaluation of the use of rifampin in nonrandomized studies with sample sizes that are inadequate to evaluate efficacy.
- May have lower hepatotoxicity than INH
- Significant drug interactions
  - Rifampin babies

Department of Public Health

Blumberg, Ann Int Med 2008;149:761

## Acceptable Regimens for Treatment of LTI

| Drugs | Duration (mo) | Interval | Rating* (Evidence)† HIV⁻ | HIV⁺ |
|---|---|---|---|---|
| Isoniazid | 9 | Daily | A (II) | A (II) |
| | | Twice weekly | B (II) | B (II) |
| Isoniazid | 6 | Daily | B (I) | C (I) |
| | | Twice weekly | B (II) | C (I) |
| Rifampin–pyrazinamide | 2 | Daily | B (II) | A (I) |
| | 2–3 | Twice weekly | C (II) | C (I) |
| Rifampin | 4 | Daily | B (II) | B (III) |

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.
† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

Department of Public Health

MMWR June 9,2000

## OOPS
## Rifampin and PZA toxicities

**Fatal and Severe Hepatitis Associated With Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection — New York and Georgia, 2000**

One of the recommended treatments for latent tuberculosis infection (LTBI) is a 9-month regimen of isoniazid (INH); a 2-month regimen of rifampin (RIF) and pyrazina-

Department of Public Health

## OOPS
## Rifampin and PZA toxicities

**Update: Fatal and Severe Liver Injuries Associated With Rifampin and Pyrazinamide for Latent Tuberculosis Infection, and Revisions in American Thoracic Society/CDC Recommendations — United States, 2001**

During February 12–August 24, 2001, a total of 21 cases of liver injury associated with a 2-month rifampin-pyrazinamide (RIF-PZA) regimen for the treatment of latent

Department of Public Health

MMWR August 31, 2001

## Revised Recommendations

- Use with caution and not recommended with underlying liver disease
- No more than a 2 week supply and reassess at 2,4 and 6 weeks
- Serum enzymes and bilirubin at baseline, 2, 4 and 6 weeks

Department of Public Health

MMWR August 31, 2001

## How about weekly INH/rifapentine for 3 months (TBTC Study 26)?

- Rumors are GREAT!!!
  - Equal efficacy to 9 months INH
  - Fewer Adverse Events
- But wait: INH/rifapentine were given by Directly Observed Therapy

Department of Public Health

## Roadmap

- Pathogenesis of TB
- Historical Perspective
- Epidemiology and Trends
- Tests for Latent TB
- Treatment for Latent TB
- **What makes a successful program for LTBI-Tx**

Department of Public Health

Arches National Park, Utah, March 2011

## GCDPH

- Very high acceptance and completion rate of treatment of latent infection
- (I have nothing to do with their success other than to stay out of the way and applaud).

Department of Public Health

## Pat Hilliard's List of Why they succeed

- 1. The increase in numbers of TB nurses in 2007 from 2 to 6 made a tremendous impact. Two TB nurses could barely handle the cases and contacts.
- 2. Free food!: bags of rice and beans

Department of Public Health

## Pat's List of Why they succeed

- 3. In the case of refugees, we not only take care of their TB infection, we help them understand their bills, bus schedules, their children's immunizations, etcetera.

Department of Public Health

## Pat's List of Why they succeed

4. We have one dedicated Class A/B nurse (Zonie) who has managed to build a rapport with ALL the resettlement agencies.

Department of Public Health

## Pat's List of Why they succeed

5. World Relief in High Point has allowed Susan to hold "mass starts" and they are vigilant in getting the refugees to these clinics. They are held usually monthly at WR headquarters. Susan and Doretta also go monthly for "mass refill day".

Department of Public Health

## Pat's List of Why they succeed

- 6. In High Point, the pharmacist, Peggy Fox, has always picked up the phone and called clients one day (literally) after their missed pick-up.
- 7. We work on a walk-in basis, which is ideal for our refugees who have trouble understanding what an appointment is.

Department of Public Health

## Pat's List of Why they succeed

- 9. Pre-start counseling: unhurried, and we stress it looks good for their green card (we do tell them completion is not a requirement to receive it).
- 10. We believe we are preventing future cases of TB. With all our hearts.

Department of Public Health

## Pat's List of Why they succeed

- 11. Some of us who perform refugee exams meet them for the 1st time there, and they remember those nice nurses when we bring them in for LTBI evaluation.
- 12. Sheer tenacity

Department of Public Health

## Pat's List of Why they succeed

- 13. When we are in the home to start, we sit down and accept offers of food and drink (in many of the cultures we encounter, it is considered rude not to accept). Pat has now eaten yak balls (they called them balls, yes), which looks like a fried donut hole drenched in sickly sweet syrup. It is actually cheese. YAK cheese

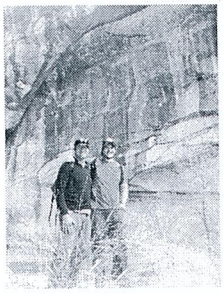
Department of Public Health

## Pat's List of Why they succeed

- 14. We just plain love TB (elimination)

Department of Public Health

## Questions?



Moab, Utah, March 2011

Department of Public Health